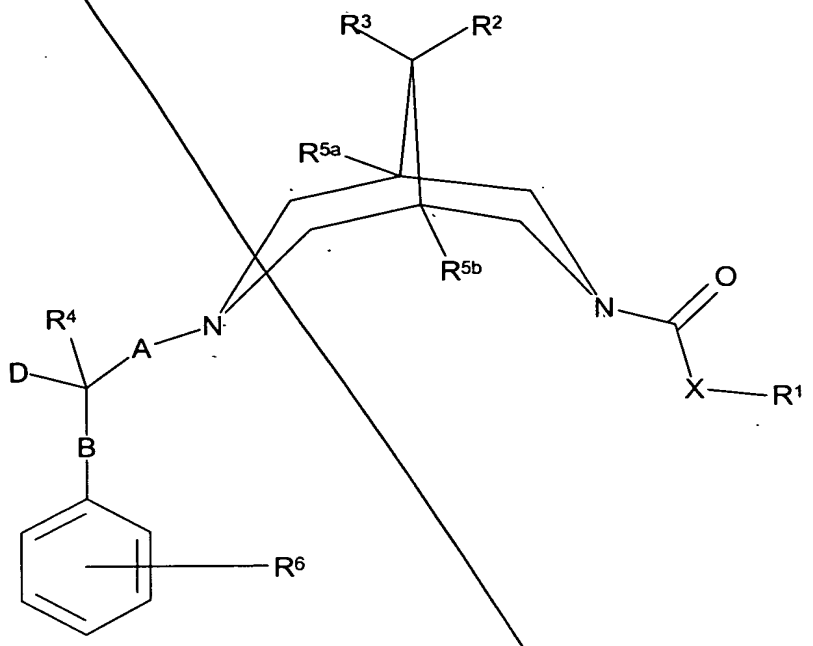
Claims

1. A compound of formula I,



I

wherein

R^1 represents C_{1-12} alkyl, $-(CH_2)_a$-aryl, or $-(CH_2)_a$-Het^1 (all of which are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

a represents 0, 1, 2, 3, or 4;

Het^1 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a} and R^{5b} independently represent H or C_{1-3} alkyl;

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R^2 and R^3 independently represent H, C_{1-4} alkyl (optionally substituted and/or terminated with one or more nitro or cyano groups), OR^7, $N(R^{7a})R^{7b}$, $OC(O)R^8$ or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;

R^7 and R^8 independently represent H, C_{1-6} alkyl or $-(CH_2)_b$-aryl (which latter two groups are optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

R^{7a} and R^{7b} independently represent H or C_{1-6} alkyl;

b represents 0, 1, 2, 3 or 4;

R^4 represents H or C_{1-6} alkyl;

D represents H, C_{1-4} alkyl, -OH, or $-(CH_2)_cN(R^{10})(R^{11})$;

c represents 0, 1, 2, 3 or 4;

R^{10} represents H, C_{1-6} alkyl, $-(CH_2)_d$-aryl, $-C(NH)NH_2$, $-S(O)_2R^{13}$, $-[C(O)]_eN(R^{14})(R^{15})$, $-C(O)R^{16}$ or $-C(O)OR^{17}$;

e represents 1 or 2;

R^{11} represents H, C_{1-6} alkyl, $-C(O)R^{18}$ or $-(CH_2)_f$-aryl (which latter group is optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{14}, R^{15}, R^{16}, R^{17} and R^{18} independently represent H, C_{1-6} alkyl, Het^2 or $-(CH_2)_g$-aryl (which latter three groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{13} represents C_{1-6} alkyl, aryl or $-(CH_2)_h$-aryl (all of which are all optionally substituted and/or terminated (as appropriate) by one or more substituents chosen from halo, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

d, f, g and h independently represent 0, 1, 2, 3 or 4;

Het^2 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^6 represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl (optionally terminated by $-N(H)C(O)OR^{18a}$), C_{1-6} alkoxy, $-C(O)N(H)R^{19}$, $-NHC(O)N(H)R^{20}$, $-N(H)S(O)_2R^{21}$ and/or $-OS(O)_2R^{22}$;

R^{19} and R^{20} independently represent H or C_{1-6} alkyl;

R^{18a}, R^{21} and R^{22} independently represent C_{1-6} alkyl;

A represents a single bond, C_{1-6} alkylene, $-N(R^{23})(CH_2)_j-$, $-O(CH_2)_j-$ or $-(CH_2)_jC(H)(OR^{23})(CH_2)_k-$ (in which latter three groups, the $-(CH_2)_j-$ group is attached to the bispidine nitrogen atom, and which latter four groups are all optionally substituted by one or more OH groups);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_mN(R^{24})-$, $-(CH_2)_mS(O)_n-$, $-(CH_2)_mO-$ (in which three latter groups, the $-(CH_2)_m-$ group is attached to the carbon atom bearing D and R^4), $-C(O)N(R^{24})-$ (in which latter group, the -C(O)- group is attached to the carbon atom bearing D and R^4), $-N(R^{24})C(O)O(CH_2)_m-$ or $-N(R^{24})(CH_2)_m-$ (in which latter two groups, the $N(R^{24})$ group is attached to the carbon atom bearing D and R^4);

j, k and m independently represent 0, 1, 2, 3 or 4;

n represents 0, 1 or 2;

R^{23} represents H, C_{1-6} alkyl or $C(O)R^{25}$;

R^{24} represents H or C_{1-6} alkyl;

R^{25} represents H, C_{1-6} alkyl, Het^3 or $-(CH_2)_p$-aryl (which latter two groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

Het^3 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

p represents 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable derivative thereof.

provided that:

(a) when D represents either H or -OH, and R^{5a} and R^{5b} both represent H, then at least one of R^2 and R^3 represents OR^7, $OC(O)R^8$ or C_{1-4} alkyl, which alkyl group is substituted and/or terminated with one or more nitro or cyano groups; and

(b) when D represents -OH or $-(CH_2)_cN(R^{10})R^{11}$ in which c represents 0, then:-

(i) A does not represent $-N(R^{23})(CH_2)_j$-, $-O(CH_2)_j$- or $-(CH_2)_jC(H)(OR^{23})(CH_2)_k$- (in which k is 0); and/or

(ii) m does not represent 0 when B represents $-(CH_2)_mN(R^{24})$-, $-(CH_2)_mS(O)_n$- or $-(CH_2)_mO$-.

2. A compound as claimed in Claim 1, wherein R^1 represents optionally substituted $-(CH_2)_a$-phenyl, in which a is 0, 1, 2 or 3, or optionally substituted, optionally unsaturated, linear, branched or cyclic, C_{1-18} alkyl (which latter group may also be interrupted by an oxygen atom).

3. A compound as claimed in any Claim 1 ~~or Claim 2~~, wherein R^2 represents H, OR^7, $-CH_2NO_2$ or $-OC(O)R^8$ or together with R^3 represents $-O-(CH_2)_2-O-$.

4. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein R^3 represents H, OR^7, C_{1-4} alkyl or together with R^2 represents $-O-(CH_2)_2-O-$.

5. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein R^4 represents H or C_{1-2} alkyl.

6. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein R^{5a} and R^{5b} either both represent H or both represent methyl.

7. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein R^6 represents one or more substituents selected from C_{1-6} alkyl, cyano, nitro, amino or $C(O)N(H)R^{19}$ or $N(H)S(O)_2R^{21}$.

8. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein X represents O.

9. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein A represents a single bond or linear, or branched, C_{1-4} alkylene (which group is also optionally interrupted by O).

10. A compound as claimed in ~~any one of the preceding claims~~ claim 1, wherein B represents a single bond, C_{1-4} alkylene, $-(CH_2)_mO-$ or $-(CH_2)_mN(R^{24})-$ (in which latter two cases m is 1, 2 or 3).

11. A compound as claimed in ~~any one of the preceding claims~~, wherein when D represents $-(CH_2)_cN(R^{10})(R^{11})$, c represents 0, 1 or 2.

12. A compound as claimed in ~~any one of the preceding claims~~, wherein when D represents $-(CH_2)_cN(R^{10})(R^{11})$, R^{10} represents H, C_{1-4} alkyl, $-C(O)R^{16}$ (in which R^{16} is H, C_{1-3} alkyl or Het^2), $-C(O)OR^{17}$ (in which R^{17} is C_{1-5} alkyl, phenyl or C_{1-3} alkylphenyl), $-C(NH)NH_2$ or $-[C(O)]_e-N(H)R^{15}$ (in which R^{15} is H or C_{1-3} alkyl).

13. A compound as claimed in ~~any one of the preceding claims~~, wherein when D represents $-(CH_2)_cN(R^{10})(R^{11})$, R^{11} represents H.

14. A pharmaceutical formulation including a compound as defined in ~~any one of Claims 1 to 13~~ in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

15. A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in ~~any one of Claims 1 to 13~~.

16. A compound as defined in ~~any one of Claims 1 to 13~~ for use as a pharmaceutical.

17. A compound as defined in ~~any one of Claims 1 to 13~~ for use in the prophylaxis or the treatment of an arrhythmia.

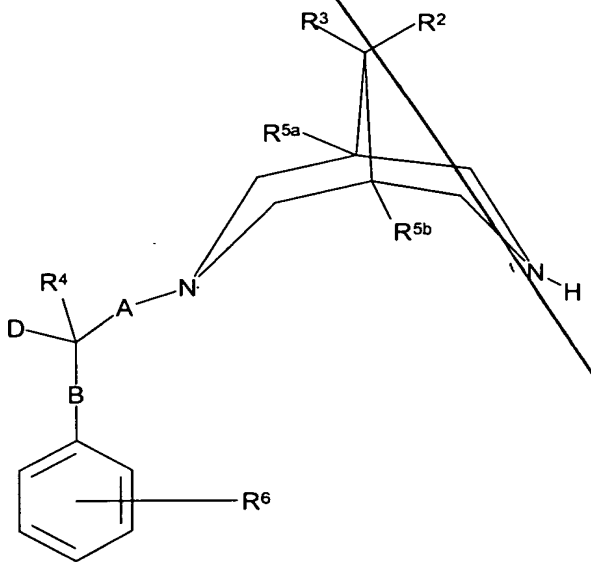
18. The use of a compound as defined in ~~any of one Claims 1 to 13~~ as active ingredient in the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

19. The use as claimed in Claim 18, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

20. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in ~~any one of Claims 1 to 13~~ Claim 1 to a person suffering from, or susceptible to, such a condition.

21. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:

(a) reaction of a compound of formula II,



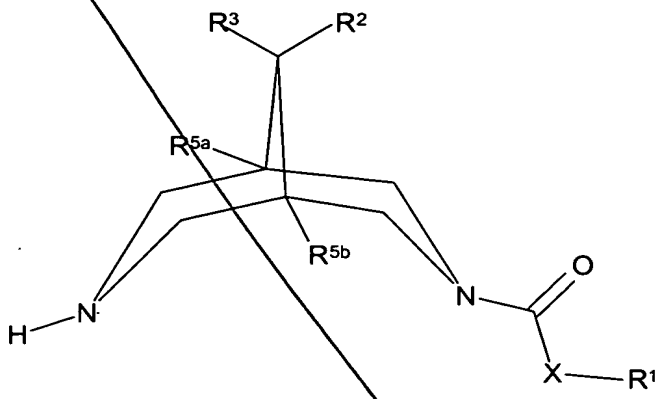
II

wherein R^2, R^3, R^4, R^{5a}, R^{5b}, R^6, A, B and D are as defined in Claim 1 with a compound of formula III,

$$R^1XC(O)L^1 \qquad \text{III}$$

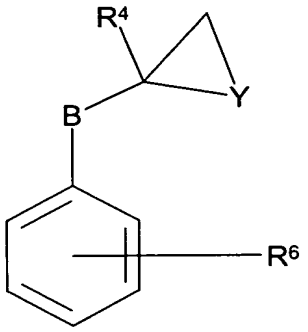
wherein L^1 represents a leaving group and R^1 and X are as defined in Claim 1;

(b) for compounds of formula I in which A represents CH_2 and D represents –OH or $N(R^{10})H$, reaction of a compound of formula IV,



IV

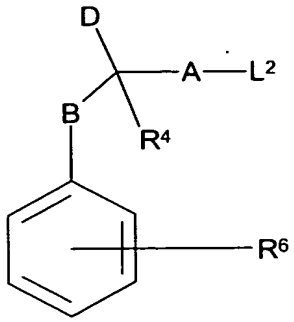
wherein R^1, R^2, R^3, R^{5a}, R^{5b} and X are as defined in Claim 1, with a compound of formula V,



V

wherein Y represents O or $N(R^{10})$ and R^4, R^6, R^{10} and B are as defined in Claim 1;

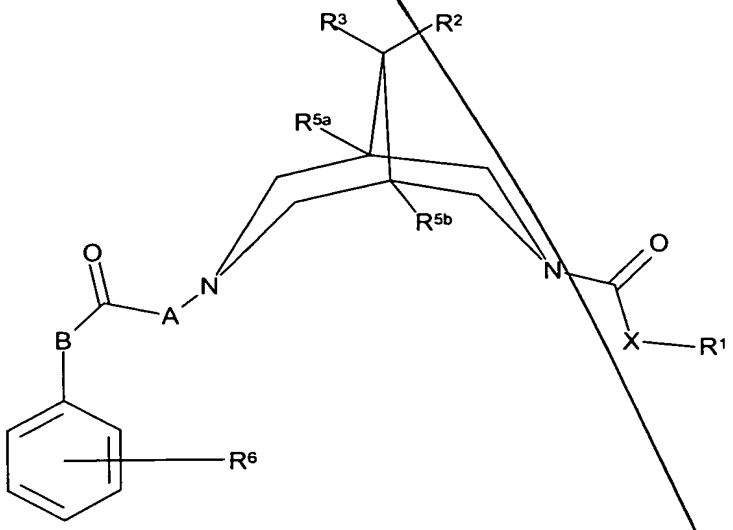
(c) reaction of a compound of formula IV, as defined above, with a compound of formula VI,



VI

wherein L^2 represents a leaving group and R^4, R^6, A, B and D are as defined in Claim 1;

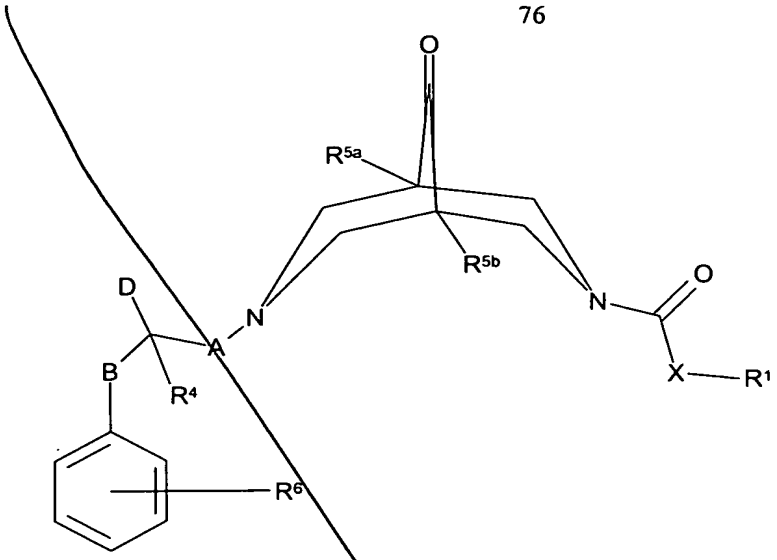
(d) for compounds of formula I in which D represents H or OH and R^4 represents H, reduction of a compound of formula VII,



VII

wherein R^1, R^2, R^3, R^{5a}, R^{5b}, R^6, A, B and X are as defined in Claim 1;

(e) for compounds of formula I in which one of R^2 and R^3 represents H or OH and the other represents H, reduction of a corresponding compound of formula VIII,



VIII

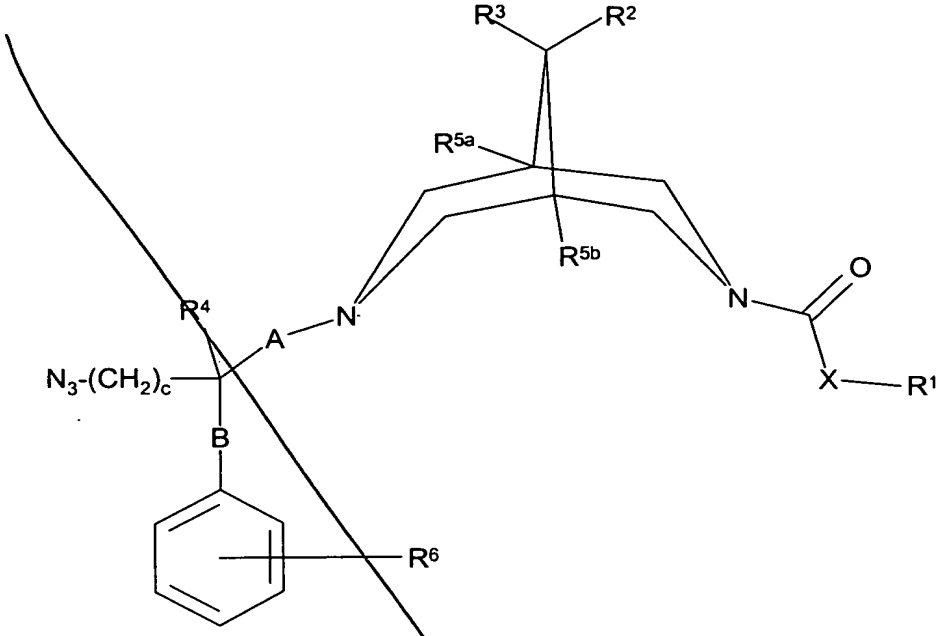
wherein R^1, R^4, R^{5a}, R^{5b}, R^6, A, B, D and X are as defined in Claim 1;

(f) for compounds of formula I in which R^2 and/or R^3 represents $OC(O)R^8$ and R^8 is as defined in Claim 1, coupling of a corresponding compound of formula I in which R^2 and/or R^3 (as appropriate) represents OH and a compound of formula VIIIA,

$$R^8CO_2H \qquad \text{VIIIA}$$

wherein R^8 is as defined in Claim 1;

(g) for compounds of formula I in which D represents $-(CH_2)_cNH_2$, reduction of a corresponding compound of formula IX,



IX

wherein c, R^1, R^2, R^3, R^4, R^{5a}, R^{5b}, R^6, A, B and X are as defined in Claim 1;

(h) for compounds of formula I in which D represents $-N(R^{11})C(O)NH(R^{15})$, in which R^{11} and R^{15} are as defined in Claim 1 except that R^{11} does not represent $C(O)R^{18}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as defined in Claim 1 except that is does not represent $C(O)R^{18}$ in which R^{18} is as defined in Claim 1, with a compound of formula X,

$$R^{15}N=C=O \qquad X$$

wherein R^{15} is as defined in Claim 1;

(i) for compounds of formula I in which D represents $-N(H)[C(O)]_2NH_2$, reaction of a corresponding compound of formula I in which D represents $-NH_2$ with oxalic acid diamide;

(j) for compounds of formula I in which D represents $-N(R^{11})C(O)R^{16}$, in which R^{11} and R^{16} are as defined in Claim 1 except that R^{11} does not represent $C(O)R^{18}$, reaction of a corresponding compound of formula I in which D represents $-N(R^{11})H$, in which R^{11} is as defined in Claim 1 except

that is does not represent $C(O)R^{18}$ in which R^{18} is as defined in Claim 1, with a compound of formula XI,

$$R^{16}C(O)R^{x} \qquad XI$$

wherein R^{x} represents a suitable leaving group and R^{16} is as defined in Claim 1;

(k) for compounds of formula I in which D represents $-N(H)R^{10}$ and R^{10} is as defined in Claim 1 except that it does not represent H or $-C(NH)NH_2$, reaction of a corresponding compound of formula I wherein D represents $-NH_2$ with a compound of formula XIA,

$$R^{10a}L^{1} \qquad XIA$$

wherein R^{10a} represents R^{10} as defined in Claim 1 except that it does not represent H or $-C(NH)NH_2$ and L^1 is as defined above;

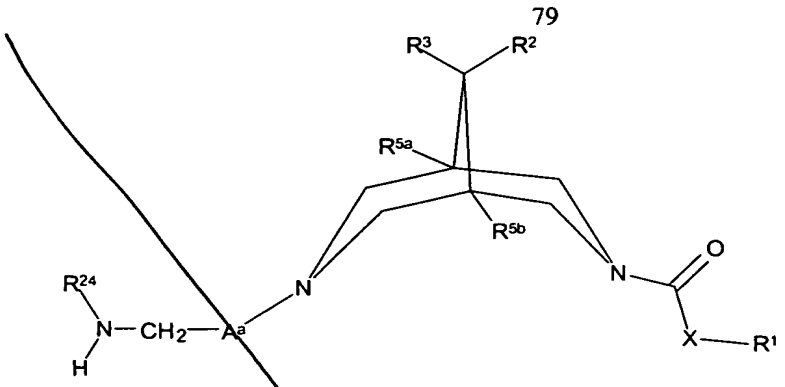
(l) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I;

(m) for compounds of formula I which are C_{1-4} alkyl quaternary ammonium salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XII,

$$R^{a}Hal \qquad XII$$

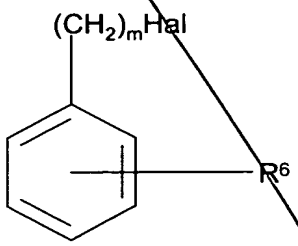
wherein R^a represents C_{1-4} alkyl and Hal represents Cl, Br or I;

(n) for compounds of formula I in which D and R^4 both represent H, A represents C_{1-6} alkylene, B represents $-N(R^{24})(CH_2)_m-$ and m and R^{24} are as defined in Claim 1, reaction of a compound of formula XIII,



XIII

wherein A^a represents C_{1-6} alkylene and R^1, R^2, R^3, R^{5a}, R^{5b}, R^{24} and X are as defined in Claim 1 with a compound of formula XIV,



XIV

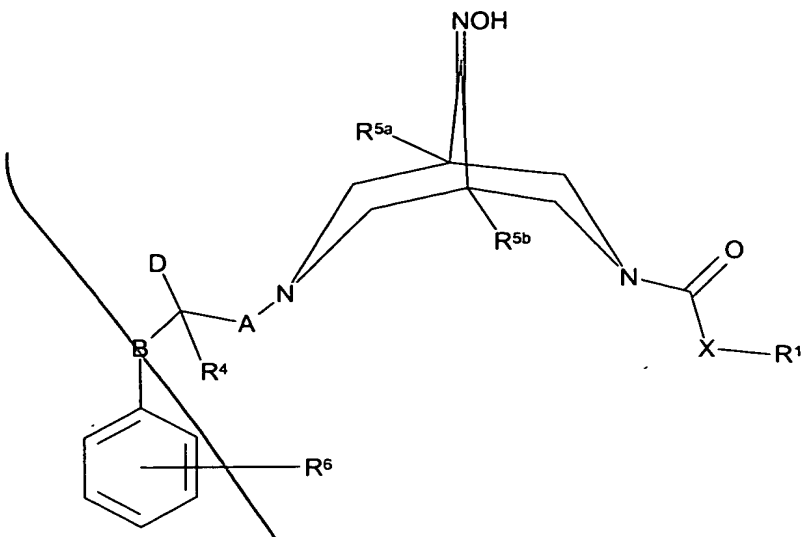
wherein R^6, m are as defined in Claim 1 and Hal is as defined above;

(o) reaction of a compound of formula II, as defined above, with a compound of formula XV,

$$R^1XH \qquad XV$$

wherein R^1 and X are as defined in Claim 1, in the presence of 1,1'-carbonyldiimidazole;

(p) for compounds of formula I in which one of R^2 and R^3 represents $-NH_2$ and the other represents H, reduction of a compound of formula XVA,



XVA

wherein R^1, R^4, R^{5a}, R^{5b}, R^6, A, B, D and X are as defined in Claim 1;

(q) for compounds of formula I in which one or both of R^2 and R^3 represent $-N(R^{7a})R^{7b}$ in which one or both or R^{7a} and R^{7b} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^2 and/or R^3 represent $-N(R^{7a})R^{7b}$ (as appropriate) in which R^{7a} and/or R^{7b} (as appropriate) represent H, using a compound of formula XXIB,

$$R^{7c}L^1 \qquad \text{XXIB}$$

wherein R^{7c} represents C_{1-6} alkyl and L^1 is as defined above;

(r) conversion of one R^6 substituent to another; or

(s) deprotection of a protected derivative of a compound of formula I as defined in Claim 1.

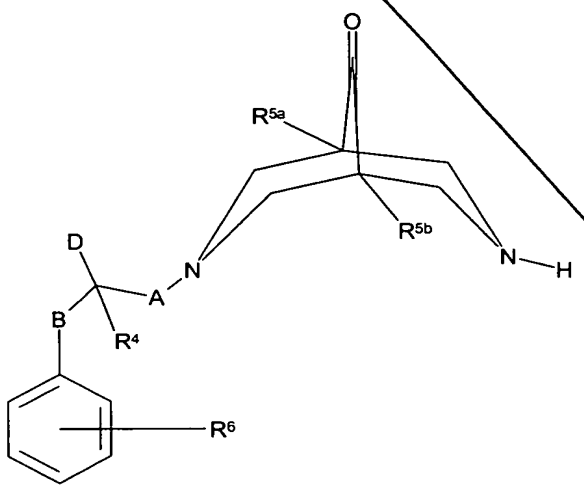
22. A compound of formula II as defined in Claim 21, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then D does not represent H or OH.

23. A compound of formula IV as defined in Claim 21, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then at least one of R^2 and R^3 represents OR^7, $OC(O)R^8$ or C_{1-4} alkyl, which alkyl

group is substituted and/or terminated with one or more nitro or cyano groups.

24. A compound of formula VIII as defined in Claim 21, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then D does not represent H or OH.

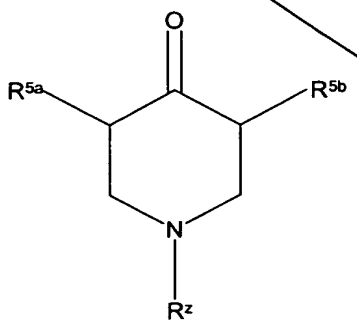
25. A compound of formula XVII,



XVII

wherein R^4, R^{5a}, R^{5b}, R^6, A, B and D are as defined in Claim 1, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then D does not represent H or OH.

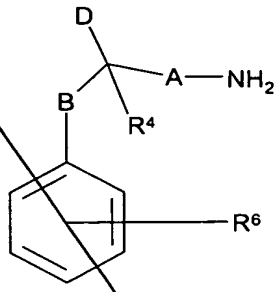
26. A process for the preparation of a compound of formula VIII, XVII, XVIII or XXVIII, as defined herein, which comprises reaction of a compound of formula XXIX,



XXIX

wherein R^z represents H or -C(O)XR^1 and R^1, R^{5a}, R^{5b} and X are as defined in Claim 1 with (as appropriate) either:

(1) a compound of formula XXX,



XXX

or a protected derivative thereof, wherein R^4, R^6, A, B and D are as defined in Claim 1; or

(2) NH_3 (or a protected derivative thereof),

in all cases in the presence of a formaldehyde.